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Tagged Cine Magnetic Resonance Imaging to Quantify Regional Mechanical Changes after Acute Myocardial Infarction

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Abstract

Purpose: The conventional volumetric approaches of measuring cardiac function are load-dependent, and are not able to discriminate functional changes in the infarct, transition and remote myocardium. We examined phase-dependent regional mechanical changes in the infarct, transition and remote regions after acute myocardial infarction (MI) in a preclinical mouse model using cardiovascular magnetic resonance imaging (CMR).

Methods: We induced acute MI in six mice with left anterior descending coronary artery ligation. We then examined cardiac (infarct, transition and remote-zone) morphology and function utilizing 9.4 T high field CMR before and 2 weeks after the induction of acute MI. Myocardial scar tissue was evaluated by using CMR with late gadolinium enhancement (LGE). After determining global function through volumetric analysis, regional wall motion was evaluated by measuring wall thickening and radial velocities. Strain rate imaging was performed to assess circumferential contraction and relaxation at the myocardium, endocardium, and epicardium.

Results: There was abnormal LGE in the anterior walls after acute MI suggesting a successful MI procedure. The transition zone consisted of a mixed signal intensity, while the remote zone contained viable myocardium. As expected, the infarct zone had demonstrated severely decreased myocardial velocities and strain rates, suggesting reduced contraction and relaxation function. Compared to pre-infarct baseline, systolic and diastolic velocities (v_S and v_D) were significantly reduced at the transition zone (v_S : -1.86 ± 0.16 cm/s vs -0.68 ± 0.13 cm/s, $P < 0.001$. v_D : 1.86 ± 0.17 cm/s vs 0.53 ± 0.06 cm/s, $P < 0.001$) and remote zone (v_S : -1.86 ± 0.16 cm/s vs -0.65 ± 0.12 cm/s, $P < 0.001$. v_D : 1.86 ± 0.16 cm/s vs 0.51 ± 0.04 cm/s, $P < 0.001$). Myocardial peak systolic and diastolic strain rates (SR_S and SR_D) were significantly lower in the transition zone (SR_S : -4.2 ± 0.3 s⁻¹ vs

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$-1.3 \pm 0.2 \text{ s}^{-1}$, $P < 0.001$. SR_D : $3.9 \pm 0.3 \text{ s}^{-1}$ vs $1.3 \pm 0.2 \text{ s}^{-1}$, $P < 0.001$) and remote zone (SR_S : $-3.8 \pm 0.3 \text{ s}^{-1}$ vs $-1.4 \pm 0.3 \text{ s}^{-1}$; $P < 0.001$. SR_D : $3.5 \pm 0.2 \text{ s}^{-1}$ vs $1.5 \pm 0.4 \text{ s}^{-1}$; $P = 0.006$). Endocardial and epicardial SR_S and SR_D were similarly reduced in the transition and remote zones compared to baseline.

Conclusions: This study, for the first time, utilized state-of-the art high-field CMR algorithms in a preclinical mouse model for a comprehensive and controlled evaluation of the regional mechanical changes in the transition and remote zones, after acute MI. Our data demonstrate that CMR can quantitatively monitor dynamic post-MI remodeling in the transition and remote zones, thereby serving as a gold standard tool for therapeutic surveillance.

Keywords

Cardiovascular magnetic resonance imaging; myocardial infarction; left ventricular remodeling; strain imaging

1. Introduction

Although recent improvements in the treatment of acute myocardial infarction (MI), such as early revascularization, have improved survival outcomes, the incidence of heart failure (HF) has increased due to progressive cardiac remodeling [1, 2]. After a sudden myocardial tissue injury has occurred, the ventricles often respond by dilating and the damaged cardiomyocytes are replaced by fibroblasts and collagen fibers [3–7]. The combined pathological processes of myocardial injury and repair contribute to negative long-term outcomes associated with ischemic cardiomyopathy. As a result, treatment plans that target the remodeling process and avert the loss of myocardial function arising from adverse adaptations can improve health outcomes and prevent heart failure.

Currently, the conventional therapies for adverse remodeling, including stem cell therapy, have been limited to the scar region and reducing the infarct size [8]. Unfortunately, the infarcted region consists of irreversible fibrosis and is not contractile for practical purposes. However, the adjacent and remote noninfarcted regions are increasingly being recognized as viable components of the myocardium [9]. In particular, the viable noninfarcted myocardium is an important target for monitoring therapies, as it is negatively affected by increased wall stress and higher oxygen demand arising from left ventricular dilation [10]. Understanding the impact of adverse remodeling on these regions could be crucial for improving myocardial function.

Cardiac function is commonly evaluated by using volumetric measures, such as the left ventricular ejection fraction (LVEF) [11]. While LVEF is clinically important for the diagnosis and management of HF, this parameter provides an indirect and load-dependent evaluation of global myocardial contraction [12]. Additionally, volumetric measures are not sensitive enough to detect subtle and early changes in myocardial function. Imaging and analysis of myocardial mechanics can provide more comprehensive insights into cardiac function [13]. Myocardial mechanics can be analyzed by evaluating changes in wall motion and deformation [14]. Wall motion may be observed by measuring relative changes in myocardial wall thickness during systole and diastole. Another metric is to evaluate

myocardial velocities, which offers additional information about the initial generation of contraction and relaxation forces [15]. Strain rate imaging provides more direct measurements of myocardial function by measuring regional changes in deformation. Strain can be intuitively defined by using a Lagrangian reference frame, whereby displacements are calculated at fixed material points in the myocardial tissue, with the deforming myocardium itself serving as a reference [16]. Strain rate can be measured by calculating the time derivative of strain, and thus offers useful physical insights into regional systolic and diastolic function [17, 18].

Cardiac imaging provides important quantitative examination of myocardial structure and function and can be used to characterize the adverse remodeling processes. A commonly used imaging modality is transthoracic echocardiography, due to its clinical utility and affordability. Tissue Doppler echocardiography (TDE) is useful for calculating strain from myocardial velocity gradients, but suffers from problems of geometric assumptions. While speckle tracking echocardiography (STE) also calculates strain and mitigates the problems of geometric assumptions, they struggle with inter-vendor variability [19]. Cardiovascular magnetic resonance imaging (CMR) remains a gold standard for evaluating myocardial structure and function due to its high accuracy and reproducibility. High-field CMR imaging results in higher spatial resolution due to increased signal-to-noise ratio [20]. Supplementing CMR with late gadolinium enhancement (LGE) allows for the characterization of myocardial viability by distinguishing regions of scar from viable myocardium [21]. A special CMR technique called myocardial tissue tagging is useful for evaluating regional deformation by tracking movements of tags, or noninvasive markers generated from locally induced perturbations of magnetization [22, 23]. These methods help to visualize and quantify changes in regional function during the cardiac cycle and illustrate the pathophysiology behind adverse remodeling.

In this study, we carried out a comprehensive, phase-dependent analysis of myocardial function after acute MI using high-field CMR. We used LGE-CMR to quantify extent of myocardial scar and characterize post-infarct myocardial regions based on the American Heart Association (AHA) segmentation model [24]. In addition, we utilized tagged cine CMR to measure regional wall thickness, myocardial velocities, circumferential strain and strain rates in the myocardium. Moreover, we evaluated endocardial and epicardial circumferential strain and strain rates to analyze layer-specific remodeling changes in contraction and relaxation at the infarct, transition and remote regions of the left ventricle.

2. Methods

2.1 Induction of Acute Myocardial Infarction

All pre-clinical procedures and protocols conformed to institutional guidelines for the care and use of animals in research and were reviewed and approved by the University at Buffalo Institutional Animal Care and Use Committee (IACUC). Acute myocardial infarction (MI) was induced in mice (age 14–15 weeks, C57B1/6 background, N = 6) by using our study protocol described previously [25, 26].

Mice underwent permanent ligation of the left anterior descending (LAD) coronary artery producing an infarct in the anterior/anteroseptal walls of the LV. Concisely, mice were anesthetized with ketamine (1 mg/kg intramuscular) and xylazine (5 mg/kg subcutaneous), and were intubated to undergo a ligation procedure (9–0 nylon) of the left anterior coronary artery. The chest wall was closed with 5–0 silk sutures, and the mice were left to recover at 30°C. To minimize discomfort, distress, and keep the pain to an absolute minimum, all studies were performed on anesthetized (1.5% of isoflurane) animals. Mice were continuously observed during procedure and for at least 1 hour into recovery. Euthanasia procedure conformed to the guidelines from the Panel on Euthanasia of the American Veterinary Medical Association. A schematic diagram of our experimental protocol is depicted in Figure 1.

2.2 CMR Imaging

We used a 20 cm diameter horizontal-bore 9.4 Tesla magnet (Biospec 94/20 USR, Bruker Biospin) equipped with a gradient coil supporting 440 mT/m gradient strength and 3440 T/m/s maximum linear slew rate (BGA-12S HP; Bruker Biospin). The scanner was operated with ParaVision (version 6.0.1; Bruker Biospin). We employed a cross-coil configuration with a 2×2-channels mouse cardiac signal reception-coil suitable for mouse cardiac studies (Bruker Biospin, T20028V3). We used generic, larger volume (86 mm) circular polarized coil for the signal transmission. We induced anesthesia with 3–4% isoflurane in 1 l/min of 100% medical-grade oxygen and maintained it during magnetic resonance imaging (MRI) with 1–3% isoflurane. We placed a tail-vein catheter (shortened to 20 µl dead volume; SAI Infusion Technologies) attached to a 300 µl insulin syringe via blunt needle filled with 2 µl/g body weight of 0.15M solution of Gadavist (Bayer HealthCare Pharmaceuticals Inc.). Once mice were placed on the MRI animal bed, respiration rate, heart rate, arterial oxygen saturation, and body temperature were monitored continuously with an SPO2-sensor attached to the animal's tail, a respiration pillow, and a rectal temperature probe (Model 1025, SA Instruments, Stony Brook, NY), respectively. The isoflurane concentration and the temperature of an integrated warm water bath in the animal bed (Thermo Fisher Scientific, Waltham, MA) were regulated to keep the respiration rate around 35–40 breaths/minute and the core body temperature between 35.5 and 36°C. A series of three orthogonal gradient echo (GRE) scout images of the heart was acquired. For the tagged images, we acquired ECG and respiration-gated axial views of the heart in cine mode with 2D SPAMM tagging (0.1mm thickness; 0.5mm grid distance) using a single-slice fast low-angle shot (FLASH) sequence with the following parameters: 2ms Gaussian pulse for slice selection; 30° flip angle; TE/TR=2.2/15ms; 50kHz readout bandwidth; fat suppression; 1mm slice thickness; 30×30mm² field of view; 256×256 matrix; 8 averages; 8 cardiac movie frames. The scan time was between 10 and 15 minutes, depending on respiration and heart rate.

For the LGE-CMR, we discharged the syringe and acquired late contrast enhancement data at 20 minutes after the injection using an ECG and respiration-gated inversion-recovery T₁-weighted FLASH sequence with the following parameters: 60° flip angle; TE/TR=2.1/1200ms; 65kHz readout bandwidth; TI=200ms; 8 axial slices with 0.8mm thickness and 0.2mm gap; 25×25mm² field of view; 256×256 matrix; no averages. The scan time was between 3 and 5 minutes, depending on respiration and heart rate. CMR images were taken

both before and after the MI induction procedure (median time = 2 weeks), which were denoted as pre-MI and post-MI images respectively.

2.3 Evaluation of Left Ventricular Function

Quantification of left ventricular (LV) volumes and function was made by using the freely available software Segment version 2.2 R6901 (<http://segment.heiberg.se>) [27]. The endocardial and epicardial borders were first identified by using short-axis cine images obtained at the level of mid-papillary muscles. With the mid-septum as a reference rotation point, the average radii and diameters were measured by using 6 different myocardial segments (anterior, anteroseptal, inferoseptal, inferior, inferolateral, anterolateral). By approximating each slice as a disc, volumes were calculated by the following formula:

$$\text{volume} = \frac{\pi}{4} * (\text{diameter})^2 * \text{slice thickness}$$

A volume vs time axis was plotted over 8–10 time increments of the cardiac cycle to generate an LV volume curve, which served as a reference to define the end systole and end diastole. Diameters and volumes were used to calculate the fractional shortening and ejection fraction for a mid-ventricular slice.

2.4 Myocardial Viability Analysis

Myocardial viability was evaluated by using short-axis late gadolinium enhancement (LGE) CMR images. After manually drawing the endocardial and epicardial borders, Segment was used to quantify myocardial scar, which is defined to consist of both the infarct core and peri-infarct zone, by using an EWA algorithm (Expectation maximization, Weighted intensity, A priori information) [28]. The EWA algorithm combines an intensity threshold determined by an expectation maximization algorithm with a pixel intensity weighted summation that accounts for partial volume effects. This algorithm also uses a priori information from coronary artery territory to aid with the automatic quantification of myocardial scar. Myocardial scar extent was assessed by using a “scar transmural area based” (STAB) method, which is based on calculating the fraction of the surface area of a myocardial segment comprising the scar, as defined by the following formula: [29]

$$\text{scar extent} = \frac{\sum \text{area scar}}{\text{segment area}}$$

Myocardial scar was then measured for all six myocardial segments, with the mid-septum serving as a reference rotation point, and datasets were exported for quantitative analyses [30]. The myocardial segment with the largest amount of scar was defined to be the infarct zone. The neighboring segments containing any amount of scar were defined to be the transition zone, while the remaining segments with no scar represented the remote zone.

2.5 Regional Wall Motion Analysis

We used Segment to quantify the amount of regional thickening in the ventricular walls. Contours were manually drawn at the endocardial and epicardial borders using short-axis

cine images obtained at the level of mid-papillary muscles. With the mid-septum serving as a reference rotation point, the average wall thickness was measured using 6 different myocardial segments. After exporting the datasets, quantitative analyses for the wall thickness (mm) were performed at end systole (WT_S) and end diastole (WT_D). Additional wall thickness parameters were calculated as follows:

$$\text{Wall Thickening}(\Delta\text{WT}) = \text{WT}_S - \text{WT}_D$$

$$\text{Fractional Wall Thickening (FWT)} = \frac{\text{WT}_S - \text{WT}_D}{\text{WT}_D} = \frac{\Delta\text{WT}}{\text{WT}_D}$$

We also examined time-dependent changes in the generation of contractile and relaxation forces by measuring myocardial radial velocities over 6 myocardial segments, with the mid-septum serving as a reference rotation point [15]. The methodology was optimized by comparing the velocity mapping algorithm with a study that measured average systolic radial velocities by Doppler echocardiogram in adult male rats [31]. Quantitative analyses for the radial velocity (cm/s) were performed at end systole (v_S) and end diastole (v_D), which corresponds to the initial generation of contractile and relaxation forces respectively.

2.6 Strain Analysis

Based on the principles of finite strain theory, myocyte contraction was examined by using a one-dimensional Lagrangian strain (ϵ) along the circumferential direction, which is defined by the following formula [23, 32, 33]:

$$\epsilon = \frac{L - L_0}{L_0}$$

Where L is the length of a myocardial segment and L₀ is the original length at end diastole.

Strain rate (SR) is defined as the time derivative of strain, which is calculated by dividing the change in strain between the two time frames (t₁ and t₂) by the time difference [23, 32, 33].

$$\text{SR} = \frac{d\epsilon}{dt} = \frac{\epsilon(t_2) - \epsilon(t_1)}{t_2 - t_1}$$

Myocardial strain was measured by using the commercially available Segment strain analysis module, which utilizes a tracking algorithm based on non-rigid image registration [34–36]. To help optimize the strain tracking algorithm, the systolic circumferential strains from pre-MI images were compared with the normal values obtained from previous CMR tagging studies [37, 38]. Myocardial circumferential strain was measured by manually drawing the endocardial and epicardial borders at end diastole, from which the software propagated the contours automatically. Endocardial and epicardial circumferential strains were similarly measured by redrawing the contours at endocardial and epicardial regions of

interest respectively and repeating the strain tracking. The quality of strain tracking was improved by manually adjusting the initial contour of the end-diastolic image and propagating again throughout the cardiac cycle. Interpolation curves were produced by averaging individual strain data together through an in-house program written in MATLAB (MathWorks, Natick, MA). Quantitative analyses for the circumferential strain (%) were performed at end systole (e_s), while quantitative analyses for the strain rate ($1/s$ or s^{-1}) were done at peak systole (SR_s) and peak diastole (SR_D), which correspond to the two peaks seen in the individual strain rate curves respectively.

2.7 Statistical Analyses

Quantitative parameters were summarized by group using the mean and standard error of the mean (SEM). Quantitative regional comparisons were made using unpaired Student's t tests. All tests were 2 sided and $P < 0.05$ was considered significant.

3. Results

3.1 Assessment of Left Ventricular Function

Two weeks after the induction procedure, acute MI resulted in dilation of the left ventricle throughout the cardiac cycle. Significant increases in the diameters were observed at end systole (baseline, 2.3 ± 0.1 mm; acute MI, 5.0 ± 0.4 mm, $P < 0.001$) and end diastole (baseline, 4.0 ± 0.1 mm; acute MI, 5.5 ± 0.3 mm, $P = 0.007$). Consequently, LV fractional shortening was significantly reduced (baseline, $43 \pm 3\%$; acute MI, $10 \pm 2\%$, $P < 0.001$). Acute MI also led to significantly higher LV volumes at end systole (baseline, 4.3 ± 0.5 mm³; acute MI, 20.1 ± 2.7 mm³, $P = 0.002$) and end diastole (baseline, 12.7 ± 0.4 mm³; acute MI, 24.1 ± 2.7 mm³, $P = 0.009$). Subsequently, acute MI resulted in significantly lower stroke volumes (baseline, 8.5 ± 0.3 mm³; acute MI, 4.0 ± 0.4 mm³, $P < 0.001$). LV ejection fraction for a mid-ventricular slice was significantly reduced after acute MI (baseline, $67 \pm 3\%$; acute MI, $18 \pm 3\%$, $P < 0.001$).

3.2 Myocardial Viability and Scar Quantification

Acute MI led to regional changes in myocardial structure and morphology due to the presence of myocardial scarring. Representative tagged CMR images depicting acute MI at systole and diastole are shown respectively in (Figure 2A and B). A representative LGE image illustrating myocardial scar is provided in (Figure 2C). The anterior wall represented the infarct zone, whereby about $95 \pm 1\%$ of the region contained myocardial scarring. The transition zone consisted of the anteroseptal and anterolateral walls, in which myocardial scar spanned about $39 \pm 5\%$ of the region ($P < 0.001$ vs infarct). The remaining regions that had no scar constituted the remote zone ($P < 0.001$ vs infarct and $P < 0.001$ vs transition) (Figure 2D).

3.3 Regional Analysis of Myocardial Wall Motion

3.3.1 Infarct Zone—When compared to pre-infarct measurements, the infarct zone had significantly lower systolic (baseline, 1.46 ± 0.09 mm; infarct, 0.56 ± 0.09 mm, $P < 0.001$) and diastolic (baseline, 0.74 ± 0.07 mm; infarct, 0.46 ± 0.05 mm, $P = 0.009$) wall thickness (Figure 3A and B). The infarct zone also experienced significant reductions in both the wall

thickening (baseline, 0.72 ± 0.07 mm; infarct, 0.10 ± 0.07 mm, $P < 0.001$) and fractional wall thickening (baseline, $103 \pm 15\%$; infarct, $25 \pm 16\%$, $P = 0.005$) (Figure 3C and D). Moreover, systolic and diastolic velocities were lower in the infarct zone compared to pre-infarct measurements (systolic velocities: baseline, -1.86 ± 0.15 cm/s; infarct, -0.61 ± 0.12 cm/s, $P < 0.001$; and diastolic velocities: baseline, 1.89 ± 0.15 cm/s; infarct, 0.46 ± 0.04 cm/s, $P < 0.001$) (Figure 4A and B).

3.3.2 Transition Zone—Compared to pre-infarct measurements, the transition zone had significantly reduced systolic (baseline, 1.47 ± 0.09 mm; transition, 0.70 ± 0.06 mm, $P < 0.001$) and diastolic (baseline, 0.75 ± 0.05 mm; transition, 0.60 ± 0.03 mm, $P = 0.040$) wall thickness (Figure 3A and B). In addition to reduced wall thickening (baseline, 0.73 ± 0.04 mm; transition, 0.11 ± 0.05 mm, $P < 0.001$), the transition zone showed significantly lower fractional wall thickening (baseline, $99 \pm 5\%$; transition, $19 \pm 9\%$, $P < 0.001$) (Figure 3C and D). Both systolic and diastolic velocities were reduced in the transitional zone compared to pre-infarct measurements (systolic velocities: baseline, -1.86 ± 0.16 cm/s; transition, -0.68 ± 0.13 cm/s, $P < 0.001$; and diastolic velocities: baseline, 1.86 ± 0.17 cm/s; transition, 0.53 ± 0.06 cm/s, $P < 0.001$) (Figure 4A and B).

3.3.3 Remote Zone—The remote zone had significantly decreased systolic wall thickness compared to pre-infarct measurements (baseline, 1.41 ± 0.10 mm; remote, 0.94 ± 0.09 mm, $P = 0.005$) (Figure 3A). However, no significant differences in the diastolic wall thickness were observed (baseline, 0.70 ± 0.03 mm; remote, 0.79 ± 0.09 mm, $P = 0.362$) (Figure 3B). In addition to decreased wall thickening (baseline, 0.71 ± 0.09 mm; remote, 0.14 ± 0.03 mm, $P = 0.001$), the remote zone displayed significantly lower fractional wall thickening (baseline, $104 \pm 15\%$; remote, $20 \pm 4\%$, $P = 0.002$) (Figure 3C and D). Furthermore, compared to pre-infarct measurements, both the systolic and diastolic velocities were significantly reduced in the remote zone (systolic velocities: baseline, -1.86 ± 0.16 cm/s; remote, -0.65 ± 0.12 cm/s, $P < 0.001$; diastolic velocities: baseline, 1.86 ± 0.16 cm/s; remote, 0.51 ± 0.04 cm/s, $P < 0.001$) (Figure 4A and B).

3.4 Strain Analysis of Myocardial Deformation

3.4.1 Temporal Changes—Representative tagged CMR images illustrating myocardial strain imaging are provided in Figure 5. Temporal changes in cardiomyocyte contraction were observed by measuring changes in circumferential strain and strain rate throughout a cardiac cycle. In pre-infarct hearts, circumferential strain uniformly decreased until it reached the negative peak strain, which corresponded to maximal circumferential shortening that occurred at systole (Figure 6A). However, acute MI resulted in the infarct and transition zones initially having positive circumferential strains at late diastole before becoming negative and reaching the peak strain. The remote zone initially remained near zero before decreasing to peak strain. For these regions, the peak strain occurred after systole (Figure 6B). Circumferential strain rates for pre-infarct hearts uniformly decreased to SR_S , after which they consistently increased to SR_D (Figure 6C). In acute MI, the circumferential strain rate initially increased in infarct, transition and remote zones, with the strain rate in infarct zone approaching close to zero, before decreasing to SR_S . The circumferential strain rates for these regions increased to SR_D , but the rate of increase was least uniform in the infarct

zone. Additionally, while acute MI did not affect the time when SR_S occurred, SR_D occurred at a time closer to end diastole than in baseline (Figure 6D).

3.4.2 Infarct Zone—Compared to pre-infarct measurements, the infarct zone had significantly lower myocardial ϵ_S (baseline, $-15.5 \pm 1.2\%$; infarct, $-1.5 \pm 0.5\%$, $P < 0.001$) (Figure 7A). Additionally, the infarct zone experienced significantly reduced myocardial SR_S (baseline, $-4.0 \pm 0.4 \text{ s}^{-1}$; infarct, $-0.5 \pm 0.1 \text{ s}^{-1}$, $P < 0.001$) and myocardial SR_D (baseline, $4.1 \pm 0.4 \text{ s}^{-1}$; infarct, $0.6 \pm 0.2 \text{ s}^{-1}$, $P < 0.001$) (Figure 7B and C).

3.4.3 Transition Zone—The transition zone had significantly reduced myocardial ϵ_S compared to pre-infarct measurements (baseline, $-16.3 \pm 0.5\%$; transition, $-4.5 \pm 0.8\%$, $P < 0.001$) (Figure 7A). In addition, the transition zone displayed significantly decreased myocardial SR_S (baseline, $-4.2 \pm 0.3 \text{ s}^{-1}$; transition, $-1.3 \pm 0.2 \text{ s}^{-1}$, $P < 0.001$) and myocardial SR_D (baseline, $3.9 \pm 0.3 \text{ s}^{-1}$; transition, $1.3 \pm 0.2 \text{ s}^{-1}$, $P < 0.001$) (Figure 7B and C).

3.4.4 Remote Zone—When compared to pre-infarct measurements, the remote zone had significantly reduced myocardial ϵ_S (baseline, $-14.5 \pm 0.4\%$; remote, $-5.5 \pm 1.4\%$, $P < 0.001$) (Figure 7A). Moreover, the remote zone had significantly lower myocardial SR_S (baseline, $-3.8 \pm 0.3 \text{ s}^{-1}$; remote, $-1.4 \pm 0.3 \text{ s}^{-1}$, $P < 0.001$) and myocardial SR_D (baseline, $3.5 \pm 0.2 \text{ s}^{-1}$; remote, $1.5 \pm 0.4 \text{ s}^{-1}$, $P = 0.006$) (Figure 7B and C).

3.5 Strain Analysis of Endocardial and Epicardial Deformation

3.5.1 Infarct Zone—Compared to pre-infarct measurements, the infarct zone had significantly reduced endocardial ϵ_S (baseline, $-26.5 \pm 1.9\%$; infarct, $-3.1 \pm 0.8\%$, $P < 0.001$) (Figure 8A). Additionally, the infarct zone experienced significantly lower endocardial SR_S (baseline, $-6.7 \pm 0.6 \text{ s}^{-1}$; infarct, $-0.9 \pm 0.2 \text{ s}^{-1}$, $P < 0.001$) and endocardial SR_D (baseline, $6.7 \pm 0.6 \text{ s}^{-1}$; infarct, $1.1 \pm 0.2 \text{ s}^{-1}$, $P < 0.001$) (Figure 8B and C). Similarly, the infarct zone had significantly reduced epicardial ϵ_S compared to pre-infarct measurements (baseline, $-5.6 \pm 0.5\%$; infarct, $-0.6 \pm 0.4\%$, $P < 0.001$) (Figure 8D). Moreover, significant decreases in both the epicardial SR_S (baseline, $-1.5 \pm 0.2 \text{ s}^{-1}$; infarct, $-0.2 \pm 0.1 \text{ s}^{-1}$, $P < 0.001$) and epicardial SR_D (baseline, $1.5 \pm 0.1 \text{ s}^{-1}$; infarct, $0.3 \pm 0.1 \text{ s}^{-1}$, $P < 0.001$) were observed in the infarct zone (Figure 8E and F).

3.5.2 Transition Zone—The transition zone had significantly lower endocardial ϵ_S compared to pre-infarct measurements (baseline, $-24.0 \pm 0.8\%$; transition, $-4.6 \pm 1.1\%$, $P < 0.001$) (Figure 8A). In addition, the transition zone had significantly reduced endocardial SR_S (baseline, $-6.2 \pm 0.5 \text{ s}^{-1}$; transition, $-1.3 \pm 0.3 \text{ s}^{-1}$, $P < 0.001$) and endocardial SR_D (baseline, $5.8 \pm 0.4 \text{ s}^{-1}$; transition, $1.4 \pm 0.3 \text{ s}^{-1}$, $P < 0.001$) (Figure 8B and C). When compared to pre-infarct measurements, the transition zone had significantly lower epicardial ϵ_S (baseline, $-10.2 \pm 0.8\%$; transition, $-4.9 \pm 0.6\%$, $P < 0.001$) (Figure 8D). Furthermore, the transition zone experienced significant reductions in both the epicardial SR_S (baseline, $-2.6 \pm 0.2 \text{ s}^{-1}$; transition, $-1.3 \pm 0.2 \text{ s}^{-1}$, $P < 0.001$) and epicardial SR_D (baseline, $2.3 \pm 0.3 \text{ s}^{-1}$; transition, $1.3 \pm 0.2 \text{ s}^{-1}$, $P = 0.031$) (Figure 8E and F).

3.5.3 Remote Zone—When compared to pre-infarct measurements, the remote zone had significantly decreased endocardial ϵ_S (baseline, $-22.2 \pm 1.0\%$; remote, $-7.9 \pm 1.8\%$, $P < 0.001$) (Figure 8A). The remote zone also had significant reductions in both the endocardial SR_S (baseline, $-5.7 \pm 0.5 \text{ s}^{-1}$; remote, $-1.9 \pm 0.3 \text{ s}^{-1}$, $P < 0.001$) and endocardial SR_D (baseline, $5.4 \pm 0.3 \text{ s}^{-1}$; remote, $2.2 \pm 0.6 \text{ s}^{-1}$, $P = 0.001$) (Figure 8B and C). Likewise, epicardial ϵ_S was significantly lower in the remote zone compared to pre-infarct measurements (baseline, $-7.9 \pm 0.4\%$; remote, $-3.2 \pm 1.0\%$, $P = 0.003$) (Figure 8D). Additionally, the remote zone had significantly reduced epicardial SR_S (baseline, $-2.2 \pm 0.1 \text{ s}^{-1}$; remote, $-0.9 \pm 0.2 \text{ s}^{-1}$, $P < 0.001$) and epicardial SR_D (baseline, $1.9 \pm 0.1 \text{ s}^{-1}$; remote, $0.9 \pm 0.3 \text{ s}^{-1}$, $P = 0.031$) (Figure 8E and F).

4. Discussion

Adverse remodeling is characterized by spatially heterogeneous changes in myocardial structure and function. Previous studies using tagged CMR compared between healthy volunteers and MI patients to suggest reduced contractility in the noninfarcted myocardium, which contributed to loss of left ventricular function [39, 40]. However, there are limited CMR studies that examined regional differences in strain and strain rate during the cardiac cycle and across cardiac layers. Additionally, novel parameters such as myocardial velocities provide important insights regarding the regional differences in the initial generation of contractile forces [15]. Our study utilized state-of-the-art, high-field CMR algorithms to comprehensively examine the regional and layer-specific mechanical changes involved in adverse remodeling. In particular, our study illustrated that although the infarct zone consisted of significantly abnormal late gadolinium enhancement suggesting of myocardial scarring, the neighboring transition and remote zones still experienced significantly reduced myocardial contraction and relaxation. Moreover, significant decreases in the endocardial and epicardial deformation were observed, indicating that the MI extended from the endocardium to the epicardium. As such, our study demonstrated that the transition and remote zones, which are viable but have reduced contractile function, could serve as important regions for monitoring therapies.

Recent studies have utilized high-field CMR algorithms to characterize the pathophysiological changes arising from myocardial infarction. In one study, Yla-Herttuala and colleagues used a rotating frame relaxation time mapping and 9.4 T CMR imaging to produce $T_{1\rho}$ and T_{RAFF2} relaxation time maps, which could accurately assess the infarct regions without the need for gadolinium contrast agents [41]. Lohöfer and colleagues combined 7 T CMR imaging with mass spectrometry imaging and Gadofluorine P validation to provide a better quantification of scar formation and extracellular matrix deposition in the infarct regions [42]. Both studies have offered useful and insightful techniques for assessing the infarct regions, which complement the conventional LGE-CMR analysis that we used for evaluating myocardial scar extent. However, these studies focused primarily on infarct size quantification and provided limited information regarding myocardial function. Our study utilized 9.4 T tagged CMR imaging to quantify regional function in the infarct, transition and remote zones. Similar to the infarct zone, the transition and remote zones, which contain viable myocardium, have reduced myocardial velocities, circumferential strain and strain rates.

CMR provides a thorough evaluation of structural and functional changes occurring in adverse remodeling, while also offering strong spatial resolution and high reproducibility. Increasing the magnetic field strength of CMR imaging improves the signal-to-noise ratio and enhances the spatial resolution. However, higher magnetic field strengths also contribute to greater susceptibility to artifacts, so the ideal range for preclinical imaging in mice is 7–11.7 T [20, 43]. Consequently, 9.4 T CMR imaging offers high quality characterization of myocardial structure and function that would be helpful in understanding the remodeling process. CMR with LGE uses extracellular gadolinium contrast agents to highlight regions of myocardial scar tissue by quantifying signal enhancement. In acute MI, the cellular necrosis in damaged cardiomyocytes disrupts the cell membranes, allowing for an increased gadolinium distribution and enhancing the scar region. LGE-CMR imaging allows for scar quantification by providing a reasonably accurate assessment of acute MI, as regions of greatest signal enhancement can reliably correspond to largest amount of myocardial scarring [21].

Tagged cine CMR imaging offers useful insights into regional myocardial function during remodeling by examining changes in contractile and relaxation properties [37]. Although volumetric methods offer important information regarding global LV function, metrics quantifying myocardial wall motion and deformation are more accurate and insightful for evaluating regional contractility [44, 45]. Wall thickness provides important information by highlighting regions of thinning, which are susceptible to increased wall stress [46]. Myocardial velocities offer useful information regarding the initial generation of contractile and relaxation forces, which are related to myocardial geometry, elasticity and fiber structure that can be affected by adverse remodeling [15, 47, 48]. Additionally, Lagrangian circumferential strains provide intuitive insights of myocardial contractility, since they utilize the deforming myocardium itself as a reference to examine regional changes in circumferential shortening across the cardiac cycle [16, 32]. Strain rate measures the rate at which these deformations occur, and parameters such as SR_S and SR_D provide reasonable noninvasive measures of regional contraction and relaxation respectively [17, 18, 49].

Post-infarct adverse remodeling is commonly characterized by infarct expansion, which occurs within hours of cardiomyocyte injury and contributes to regional wall thinning, increased wall stress and ventricular dilation [50, 51]. From LGE-CMR imaging, the infarct zone consisted of the anterior wall that had the strongest signal enhancement, which suggested significant myocardial scarring. In our study, the infarct zone was markedly thin and least contractile, thus acting as a passive segment. From diastole to late diastole, the infarct zone displayed dyskinetic motion by circumferentially bulging outwards. Given the minimal contraction of the infarct zone, the dyskinetic motion could be attributed to tethering effects, whereby the adjacent transition zone might have transferred strain to the infarct zone resulting in its contraction [52, 53]. After late diastole, the infarct zone showed reduced shortening for the remaining of the cardiac cycle.

The transition zone consists of the two myocardial walls that border the infarct zone and serves as an intermediate region between the infarct zone and remote zone. This region contains the peri-infarct zone, which is characterized by having an intermediate CMR intensity level that corresponds to a region containing a mixture of viable and non-viable

cells and being a predictor of post-MI mortality [54, 55]. From LGE-CMR imaging, the transition zone consisted of the anteroseptal and anterolateral walls that had moderate signal enhancement, which indicated intermediate levels of myocardial scarring. The transition zone had reduced wall thickening and lower contractile and relaxation velocities. From diastole to late diastole, the transition zone displayed dyskinetic motion by circumferentially bulging outwards. The pathological mechanism could be attributed to tethering effects that operated in a bidirectional manner between the infarct zone and transition zone [52, 53]. The strain transfer from the transition zone to the infarct zone might have resulted in the infarct zone having a temporary reaction force that pulled the transition zone outwards initially. Since the transition zone still had contractile function, the initial bulging lasted for a shorter time compared to that of the infarct zone. After late diastole, the transition zone experienced reduced shortening for the remaining of the cardiac cycle.

The remote zone contains the viable myocardium that is distant from the infarct zone. From LGE-CMR imaging, the remote zone consisted of the inferior, inferoseptal and inferolateral walls that contained no scarring and lacked signal enhancement. However, while myocardial scarring was not apparent, the remote zone showed different mechanical properties than expected for a healthy myocardium. The remote zone had reduced wall thickening and lower contractile and relaxation velocities. The remote zone also demonstrated hypokinetic motion throughout the cardiac cycle, but during the time from diastole to late diastole, the remote zone's motion was approximately akinetic. It is possible that adverse remodeling in the infarct zone might have spilled over throughout the myocardium and contributed to reduced contraction in remote zone [53].

The adverse remodeling processes affecting the myocardium also contributed to pathological changes in the endocardium and epicardium. Circumferential strain normally increases from the epicardium to the endocardium [23, 56]. This trend was observed in the infarct zone and remote zone but it was markedly reduced in the transition zone. The consistent reductions in endocardial strain and strain rates across the infarct, transition and remote zones could be explained by the susceptibility of the endocardium to ischemia. However, similar reductions in strain and strain rate were also observed in the epicardium. This suggested that MI operated through a “wavefront phenomenon” whereby the necrosis spread from the endocardium towards the epicardium, which occurred when the coronary occlusion was prolonged [53, 57]. As such, the adverse remodeling process likely contributed to significant mechanical changes that had occurred throughout the left ventricle wall.

A significant limitation to this study is that short-axis CMR images were taken for only the mid-ventricular slice. Having additional slices and performing long-axis imaging would provide more comprehensive insights into the regional variation of mechanical function, allow for an accurate calculation of the ejection fraction, and offer additional data regarding longitudinal strain, twisting and torsion. Another limitation is low temporal resolution of CMR imaging. CMR images were taken on average of 8–10 timeframes, which might affect the accuracy of strain rates. Moreover, only circumferential strain was calculated, as the small number of tags spanning along the myocardial wall led to imprecise and inaccurate measurements of radial strain. Instead, wall thickening parameters were used to quantify

wall motion in the radial direction. The fading of myocardial tags near the epicardial border contributed to variation in the epicardial circumferential strain and strain rates.

5. Conclusion

Our study showed that adverse cardiac remodeling resulted in significant changes in mechanical function in the transition and remote zones. Additional translational studies exploring these changes will provide useful clinical insights into the remodeling process and guide the development of new therapeutic strategies.

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Abbreviations

CMR	Cardiovascular magnetic resonance
EF	Ejection fraction
HF	Heart failure
LGE	Late gadolinium enhancement
LV	Left ventricle
MI	Myocardial infarction
MRI	Magnetic resonance imaging

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Figure 1. 6-segment American Heart Association (AHA) model illustrating the induction of acute myocardial infarction for a mid-ventricular slice.

The left-ventricular rotation line is rotated to mid-septum. The segment with the largest amount of scar tissue is defined as the infarct zone. The segments neighboring the infarct zone correspond to the transition zone, and the remaining three segments define the remote zone. AS = anteroseptal; AN = anterior; AL = anterolateral; IL = inferolateral; IN = inferior; IS = inferoseptal; IZ = infarct zone; TZ = transition zone; RZ = remote zone.

Figure 2. Assessment of myocardial scar using cardiac magnetic resonance imaging (CMR). **A-B**, Representative short-axis tagged images illustrating myocardial infarction. **A**, End systole. **B**, End diastole. **C**, Representative short-axis late gadolinium enhancement (LGE) CMR image with scar regions highlighted; red areas indicate the infarct core; and yellow areas depict the gray (peri-infarct) zone; **D**, Quantification of myocardial scar in infarct, transition and remote zones. Data are represented in terms of mean $\pm$ SEM (standard error of the mean). *Indicates $p < 0.001$ when compared to infarct zone, and # indicates $p < 0.001$ when compared to transition zones, $N = 6$.

Figure 3. Comparison of regional variation in wall thickness parameters before (Pre-MI) and after (Post-MI) the induction of acute myocardial infarction. A, Bar diagrams comparing wall thickness at end systole; B, wall thickness at end diastole; C, wall thickening; D, fractional wall thickening. Data are represented in terms of mean $\pm$ SEM (standard error of the mean). *Indicates $p < 0.05$ when comparing Post-MI to Pre-MI, $N = 6$.

Figure 4. Analysis of regional variation in radial velocities before (Pre-MI) and after (Post-MI) the induction of acute myocardial infarction.

A, Bar diagrams comparing end-systolic radial velocities, which are shown in the negative axis due to cardiomyocyte shortening (contraction); **B**, end-diastolic radial velocities, which are shown in the positive axis due to cardiomyocyte lengthening (relaxation). Data are represented in terms of mean $\pm$ SEM (standard error of the mean). *Indicates $p < 0.05$ when comparing Post-MI to Pre-MI, $N = 6$.

Figure 5. Strain visualization of the induction of acute myocardial infarction (MI) using cardiac magnetic resonance imaging (CMR) with tissue tagging.

A-B, Representative short-axis tagged images before MI induction. **A**, End systole. **B**, End diastole. **C-D**, Representative short-axis tagged images after MI induction. **C**, End systole. **D**, End diastole.

Figure 6. Strain curves illustrating regional changes in circumferential strain and strain rate over the course of a cardiac cycle.

Strain curves were produced by averaging the strain values measured at each time point. **A-B**, circumferential strain curves before and after myocardial infarction. The minimal point is the peak strain; **A**, peak strain is located at end systole; **B**, peak strain occurs after end systole, suggesting asynchronous contractions; **C-D**, circumferential strain rate curves before and after myocardial infarction. The minimal point is the peak systolic strain rate, while the maximal point is the peak diastolic strain rate.

Figure 7. Analysis of regional variation in circumferential strain and strain rates in the myocardium before (Pre-MI) and after (Post-MI) the induction of acute myocardial infarction. A-C, bar diagrams measuring peak strain and strain rate parameters, which are found by averaging the peak values for individual strain curves. Peak systolic strains are shown in negative axis because of circumferential shortening (contraction). peak diastolic strain is shown in positive axis because of circumferential lengthening (relaxation); A, peak systolic myocardial strain; B, peak systolic myocardial strain rate; C, peak diastolic myocardial strain rate. Data are represented in terms of mean $\pm$ SEM (standard error of the mean). *Indicates $p < 0.05$ when comparing Post-MI to Pre-MI, $N = 6$.

Figure 8. Assessment of regional variation in circumferential strain and strain rates in the endocardium and epicardium before (Pre-MI) and after (Post-MI) the induction of acute myocardial infarction.

A-F, bar diagrams measuring peak strain and strain rate parameters. Peak systolic strains are shown in negative axis due to circumferential shortening (contraction). peak diastolic strain is shown in positive axis due to circumferential lengthening (relaxation); **A**, peak systolic endocardial strain; **B**, peak systolic endocardial strain rate; **C**, peak diastolic endocardial strain rate; **D**, peak systolic epicardial strain; **E**, peak systolic epicardial strain rate; **F**, peak diastolic epicardial strain rate. Data are represented in terms of mean ± SEM (standard error of the mean). *Indicates $p < 0.05$ when comparing Post-MI to Pre-MI, $N = 6$.